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# **Effect of adalimumab on visual functioning in patients with non-infectious intermediate, posterior, and panuveitis in the VISUAL-1 and VISUAL-2 trials.**

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## Abstract

**Importance:** Adalimumab was recently approved for the treatment of non-infectious intermediate, posterior, and panuveitis. This study quantifies the effect of adalimumab on patient-reported visual functioning.

**Objective:** To assess the effect of adalimumab on the visual functioning and quality of life in subjects with corticosteroid dependent non-infectious intermediate, posterior, and panuveitis.

**Design:** A post-hoc analysis of clinical trials of adults with active (VISUAL-1) and inactive (VISUAL-2) non-infectious intermediate, posterior, and panuveitis.

**Setting:** Study sites were located in the United States, Canada, Europe, Israel, Australia, Latin America and Japan.

**Participants:** A total of 217 subjects (110 adalimumab, 107 placebo) in VISUAL-1, and 226 subjects (115 adalimumab, 111 placebo) in VISUAL-2, were studied using intent-to-treat analyses.

**Interventions:** In VISUAL-1 and VISUAL-2, patients were randomized to receive adalimumab (80mg loading dose followed by 40mg every other week) or placebo for 80 weeks. All patients underwent prednisone tapering, with patients in VISUAL-1 receiving an initial prednisone burst.

**Main Outcomes and Measures:** The VFQ-25 composite score questionnaire assessed the impact of visual impairment from the patient's perspective. The change in VFQ-25 from best state achieved prior to Week 6 (VISUAL-1) and from baseline state (VISUAL-2) to the final / early termination visit was determined in each group and statistically compared using ANOVA. Additionally, the temporal effects of adalimumab and placebo on VFQ-25 were investigated using a longitudinal model.

### Results:

In VISUAL-1, the change from final score to best score in VFQ-25 was -1.30 for adalimumab and -5.50 for placebo, a clinically and significantly meaningful difference of 4.20 (CI: 1.04-7.36; P=0.010) associated with adalimumab relative to placebo. In VISUAL-2, the difference between final score and baseline score in VFQ-25 was 2.12 (-0.81-5.04; P=0.16) higher for adalimumab. In both trials, the longitudinal models showed a significant difference in VFQ-25 between adalimumab and placebo of 3.07 (CI:2.09–4.06; P<0.001) and 4.66 (CI:0.05-9.26; P=0.048) by the end of the VISUAL-1 and VISUAL-2 trials, respectively.

**Conclusions and Relevance:** Adalimumab is associated with statistically significant and clinically meaningful improvements in visual functioning for subjects with non-infectious intermediate, posterior, and panuveitis.

**Trial Registration:** clinicaltrials.gov Identifiers: NCT01138657 and NCT01124838

## Manuscript Body

### INTRODUCTION

Non-infectious uveitis is a group of intraocular inflammatory disorders. Patients with uveitis can experience significant visual impairment that may result in partial or complete loss of vision.<sup>1</sup> The annual incidence of uveitis has been estimated to be between 17-52 per 100,000 individuals.<sup>2</sup> In particular, uveitis is responsible for an estimated 10% of cases of blindness in the United States,<sup>2,3</sup> including 30,000 new cases of legal blindness each year.<sup>4</sup> Uveitis can affect people of any age, but it most commonly affects people between the ages of 20 and 59 years and it is a major cause of visual morbidity in the working age group.<sup>5</sup> The impact of disease is significant in terms of healthcare utilization and costs<sup>6</sup> as well as ocular morbidity.<sup>7</sup>

The Standardization of Uveitis Nomenclature criteria categorizes uveitis based on the primary anatomical location of inflammation.<sup>8</sup> Anterior uveitis is the most common type of uveitis and accounts for 50%-90% of all cases of uveitis.<sup>9-11</sup> Intermediate and posterior uveitis account for 1%-15% and 4%-19% of uveitis cases, respectively.<sup>10-12</sup> Patients with untreated intermediate and posterior uveitis are at increased risk of developing significant and sometimes permanent vision loss.<sup>12</sup> In fact, posterior uveitis accounts for more vision loss than the other more prevalent forms of uveitis.<sup>13</sup>

The primary standard of care for uveitis is corticosteroids. However, chronic use of moderate to high doses of corticosteroids to treat uveitis can result in serious adverse events, including both ocular morbidity such as glaucoma, cataracts, and systemic adverse events including impaired glucose tolerance, hypertension, osteoporosis, and infections.<sup>14-16</sup>

Adalimumab, an anti-inflammatory drug that binds to tumor necrosis factor-alpha, was recently approved for the treatment of non-infectious intermediate, posterior, and panuveitis. Two phase 3 clinical trials, VISUAL-1 and VISUAL-2, have been conducted among active and inactive uveitis patients, respectively. Specifically, VISUAL-1 assessed clinical outcomes in patients requiring 10-60mg of oral prednisone (or oral corticosteroid equivalent) for active non-infectious intermediate, posterior, and panuveitis, while VISUAL-2 assessed clinical outcomes for patients with inactive non-infectious intermediate, posterior, and panuveitis requiring 10-35mg of oral prednisone to maintain an inactive state. In both trials, adalimumab significantly lowered the risk for uveitic flare or vision loss with low safety concerns.<sup>17,18</sup>

Uveitis has a substantial impact on individuals' physical, professional, psychological, and social functioning in day to day life. In addition to decreased vision, other commonly associated symptoms of uveitis include eye pain, redness, light sensitivity or photophobia, and floaters.<sup>19</sup> Several recent studies have focused on the impact of decreased vision and other symptoms on

quality of life outcomes among uveitis patients.<sup>20-25</sup> Given that both uveitis and corticosteroid therapy are related to increased likelihood of complications, it may be difficult to determine disease versus treatment effect on co-morbidity and quality of life. Moreover, non-infectious uveitis is associated with a number of systemic disorders including Behcet's disease, juvenile idiopathic arthritis, rheumatoid arthritis, Vogt-Koyanagi-Harada disease, sarcoidosis, ankylosing spondylitis, psoriatic arthritis, and multiple sclerosis.<sup>11,26</sup> Consequently, the impact of uveitis symptoms and associated comorbidities generally results in lower health-related and vision-related quality of life (VRQoL) as compared to healthy adults.<sup>27</sup> The objective of this research was to evaluate the effect of adalimumab beyond clinical endpoints, focusing on patient-reported VRQoL metrics.

## **METHODS**

### **Patient Population and Study Design**

The patient population consists of subjects enrolled in the VISUAL-1 and VISUAL-2 clinical trials, two phase 3, randomized, double-masked, placebo-controlled multicenter studies with parallel study designs conducted between August 2010 and May 2015. VISUAL-1 required subjects to have had active disease in at least 1 eye despite at least 2 weeks of oral prednisone (or oral corticosteroid equivalent) at a dose of 10-60mg/day. Active uveitis was defined as having at least one of the following parameters in at least one eye: active inflammatory, chorioretinal, or retinal vascular lesions;  $\geq 2+$  anterior chamber cells; and/or  $\geq 2+$  vitreous haze. To be included in VISUAL-2, subjects were required to have had inactive disease for at least 28 days prior to the baseline visit, to be taking between 10-35mg/day of oral prednisone, and to have a documented history of experiencing at least one uveitis flare within 18 months of the screening visit.

Patients in the VISUAL-1 trial were randomized to adalimumab or placebo in a 1:1 ratio via an interactive voice and web response system using a computer-generated random assignment sequence stratified by baseline immunosuppressant treatment. Patients randomized to adalimumab received an 80mg loading dose of adalimumab followed by 40mg every other week starting at week 1, patients randomized to placebo received a matching placebo according to the same schedule. Both arms also received a standardized open-label oral prednisone burst of 60mg at study entry followed by a protocol-defined mandatory taper schedule in which all subjects continuing in the study discontinued prednisone intake no later than week 15. In VISUAL-2, patients randomly received adalimumab or placebo, using a similar random assignment voice system with a block of four to assign patients. Patients were not given a burst of oral prednisone at the start of the trial, nor were patients on a uniform tapering schedule. Instead, each patient was assigned to a different schedule depending on their starting prednisone dose (10-35mg/day).

All patients discontinued oral prednisone on or before week 19 (Appendix A-C). Both trials concluded at the pre-specified 80 week time point.

The studies were conducted in accordance with the protocol, International Council for Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct, the ethical principles of the Declaration of Helsinki and all applicable local regulations. The primary efficacy and safety results from the VISUAL-1 and VISUAL-2 trials and trial protocols have been reported elsewhere.<sup>17,18</sup>

As the primary clinical endpoint of the VISUAL-1 (treatment failure) trial was assessed for the first time at Week 6, fourteen subjects (9 adalimumab and 5 placebo subjects) dropping out through Week 6 were excluded from the analysis. All other patients in the intention-to-treat (ITT) population were included in the analysis. In VISUAL-2, difference in VFQ-25 scores from baseline visit to final/early termination visit was compared between adalimumab and placebo using ANOVA. Five patients (1 adalimumab and 4 placebo subjects) did not have a baseline or final/early termination score and were excluded from this analysis.

## **Visual functioning**

The VRQoL was assessed using the National Eye Institute Vision Function Questionnaire (NEI VFQ-25), which measures important aspects of visual functioning, as well as social functioning and emotional well-being.<sup>28</sup> The VFQ-25 consists of 25 items presented in Likert scale format in which patients are asked to rate the level of severity of particular visual symptoms or difficulty of activities, such as driving or reading ordinary print in newspapers. It generates a General Health subscale, in addition to the following 11 VRQoL subscales: general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. Finally, an overall composite score is calculated, serving as an average of the 11 vision-related subscales. Scores range from 0 to 100, with higher scores indicating better VRQoL.<sup>29</sup> The reliability and validity of the NEI VFQ-25 questionnaire has been previously established in non-infectious uveitis.<sup>30-32</sup> Meaningful change thresholds were generated for each subscale of the NEI VFQ-25 using Best Corrected Visual Acuity (BCVA) categories of 5 to 9 letters.<sup>33</sup>

## **Statistical Analyses**

### ***ANOVA Analysis***

To assess the impact of adalimumab on patient reported VRQoL, the change in VFQ-25 composite score was analyzed and compared between adalimumab and placebo patients using ANOVA. In VISUAL-1, the change in VFQ-25 composite score from best state achieved prior to

Week 6 to the final/early termination visit was compared (to account for the initial corticosteroid burst). In VISUAL-2, the change in VFQ-25 composite score from baseline to the final/early termination visit was compared. To increase the sample size and the power of the results, missing values of VFQ-25 after early termination visit were imputed with the last observation carried forward (LOCF). All analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, NC) and R, version 3.1 (R Development, Vienna, Austria). The Holm-Bonferroni method was used to correct for multiple comparisons controlling the familywise error rate at 0.05.

### ***Longitudinal Analysis***

To investigate and compare the temporal effects of adalimumab and placebo on VFQ-25, in a manner that makes use of all VFQ-25 measurements per patient across time (a patient can have up to 23 VFQ-25 measurements during the trial), a generalized estimating equations (GEE) longitudinal model was used to account for correlation between repeated measurements.<sup>34</sup> The model also includes terms to capture the non-linear trajectories in VFQ-25 composite score, as well as the effect of adalimumab versus placebo. Specifically, the temporal change of VFQ-25 composite score of a patient is modeled as follows:

$$VFQ = \beta_0 + \beta_1 ADA + \beta_2 T + \beta_3 D + \beta_4 D * ADA + \epsilon \quad (1)$$

where *ADA* is a categorical variable indicating whether the patient was on adalimumab, and *T* is the number of days after randomization. In VISUAL-1, the variable *D* is set to 0 if *T* is <42 days and set to *T*-42 if *T* is ≥42 days. In VISUAL-2, *D* is set to 0 if *T* is <56 days or set to *T*-56 if *T* is ≥56 days. Lastly,  $\epsilon$  is an error term modeled with an exchangeable covariance matrix for each patient (i.e., within subject observations are equally correlated). This model formulation is parsimonious yet complex enough as to account for different temporal profiles of the VFQ-25 scores before and after day 42 and 56, respectively, and different profiles (i.e., separate slopes) for the adalimumab and placebo arms after day 42 and 56 (via the interaction term  $\beta_4 D * ADA$ ). In addition, to account for the large difference in mean VFQ-25 scores at baseline between the adalimumab and placebo arm patients in VISUAL-2, the intercept term  $\beta_1 ADA$  is included for the analysis of the VISUAL-2 data only.

Day 42 was identified as the switching point in the model of VFQ-25 for VISUAL-1 because subjects dropping out through week 6 were excluded from the analysis. Furthermore, the switching point was designed to capture the expected rise in visual functioning that patients would experience in the weeks immediately following steroid burst. Similarly, a switching point at week 8 of VISUAL-2 was included, as there were no VFQ-25 measurements at week 6, but rather at week 8. Missing values of VFQ-25 were imputed via LOCF.

## Responsiveness

To help quantify the relevance of changes in VFQ-25, thresholds for responsiveness on the VFQ-25 were derived using the BCVA response levels of  $\geq 5$  letters (minimal deterioration based on distribution-based meaningful change threshold).<sup>33</sup>

Measure	Worst BCVA Score	
	VISUAL-1	VISUAL-2
MID: Worsening of $\geq 5$ letters	$\leq -3.26$	$\leq -0.95$

Cumulative distribution function curves were calculated as cumulative change on the VFQ-25 total scores for all available changes from the best state achieved (prior to week 6) for VISUAL-1 and baseline for VISUAL-2 to subsequent time points by treatment.

## RESULTS

### VISUAL-1

Demographic and baseline characteristics of the 217 participants in the intent-to-treat population are summarized in Table 1. The mean age of the all patients was 42.7 years (standard deviation [SD]=14.9) and 57.1% were female. On average, the patients had uveitis for 45.53 months (SD=62.54) and 22% of the participants had intermediate uveitis while 33% and 45% had posterior and panuveitis, respectively. The baseline VFQ-25 composite score was 68.11.

Adalimumab treated patients had a smaller mean decline in 11 of 12 VFQ-25 scores from best score achieved before week 6 to the final/early termination visit (Figure 1). Moreover, patients treated with adalimumab also showed statistically significant improvements in the Ocular Pain ( $\Delta=10.02$ , 95% CI: 4.90-15.15; p-value<0.001) and General Vision ( $\Delta=6.20$ , 95% CI: 1.46-10.95; p-value=0.011) subcomponents. Additionally, adalimumab-treated patients had a clinically meaningful improvement relative to placebo in terms of change in VFQ-25 composite score between final and best before week 6 ( $\Delta=4.20$ , 95% CI: 1.04-7.36, p-value=0.01). Sensitivity analyses were performed comparing the difference in all scores from best score achieved before week 6 to weeks 32, 48 and 64, instead of final visit. The analyses indicate that the results do not change substantially with time (Appendix).

Figure 2a shows the mean VFQ-25 composite score over time for the adalimumab and placebo arms in VISUAL-1. The model (Table 2a) estimated that, on average, patients experienced an increase of 6.14 in VFQ-25 composite score over the first six weeks of corticosteroid burst. There was a statistically significant treatment effect on the rate of VFQ-25 decrease over time,



with the VFQ-25 scores of placebo patients declining, on average, by 0.25 ( $=30 \times (\beta_2 + \beta_3)$ ) each month after week 6 compared to an average decline of 0.08 ( $=30 \times (\beta_2 + \beta_3 + \beta_4)$ ) for adalimumab patients. The estimated mean difference in VFQ-25 composite score at week 80 between adalimumab and placebo participants was 3.07 (95% CI: 2.09–4.06;  $P < 0.001$ ).

In VISUAL-1, the proportion of patients deteriorating by statistically significant clinically relevant thresholds ( $\geq 5$ -word deterioration on the BCVA) was higher for patients on the placebo arm compared to adalimumab patients (47.06% versus 30.69%,  $p = 0.021$ ; Figure 3a).

## *VISUAL-2*

Demographic and baseline characteristics of the 226 participants in the intent-to-treat population are summarized in Table 1. The mean age of patients was 42.5 years (SD=13.4) and 61.1% were female. On average, the patients had uveitis for 61.16 months (SD=65.94), and 22% of the participants had intermediate uveitis while 33% and 45% had posterior and panuveitis, respectively. The baseline VFQ-25 was numerically (but not significantly) higher for adalimumab treated patients.

Adalimumab-treated patients had a smaller mean decline in 9 of 12 VFQ-25 scores from baseline score to the final/early termination visit (Figure 1). Patients treated with adalimumab showed statistically significant improvements in the general vision ( $\Delta = 6.46$ , 95% CI: 2.33–10.60,  $p$ -value=0.003) subcomponent. Additionally, adalimumab-treated patients had an improvement relative to placebo in terms of change between final and baseline VFQ-25 composite scores ( $\Delta = 2.12$ , 95% CI: -0.81–5.04,  $p$ -value=0.16). Sensitivity analyses performed comparing the difference in all scores from baseline to weeks 32, 48 and 64, also indicated that the results do not change substantially with time (Appendix).

Figure 2b shows the mean VFQ-25 composite score over time for the adalimumab and placebo arms in VISUAL-2. The model (Table 2b) estimated that, on average, patients experienced an increase of 2.72 in VFQ-25 composite score over the first eight weeks. As in VISUAL-1, there was a statistically significant treatment effect on the rate of VFQ-25 decrease over time, with the VFQ-25 scores of placebo patients declining, on average, by 0.126 ( $=30 \times (\beta_2 + \beta_3)$ ) each month after week 8 compared to an average decline of 0.02 ( $=30 \times (\beta_2 + \beta_3 + \beta_4)$ ) for adalimumab patients. The estimated mean difference in VFQ-25 composite score at week 80 between adalimumab and placebo participants was 4.66 (95% CI: 0.05–9.26;  $P = 0.048$ ).

In VISUAL-2, while not significant, the proportion of patients deteriorating by clinically relevant thresholds on placebo arm was higher compared to adalimumab patients (32.71% versus 23.48%;  $p = 0.137$ ; Figure 3b).

## DISCUSSION

Uveitis is one of the leading causes of ocular morbidity and blindness in the U.S. Severe uveitis often requires systemic treatment with corticosteroids or other immunosuppressive agents, which may lead to a wide array of adverse events.<sup>14-16</sup> Thus, there exists a need for alternative therapies that demonstrate not only clinical benefits and safety, but also a positive impact on the patient's VRQoL. This study demonstrates that adalimumab treatment was associated with significantly better maintenance of VFQ-25 scores compared to placebo, corroborating the positive effects of reducing the severity of uveitis symptoms in VRQoL.

Adalimumab has been associated with improved health-related quality of life (HRQoL) in patients with Crohn's disease,<sup>35</sup> psoriasis,<sup>36</sup> rheumatoid arthritis,<sup>37</sup> ankylosing spondylitis,<sup>38</sup> psoriatic arthritis,<sup>39</sup> ulcerative colitis,<sup>40</sup> and hidradenitis suppurativa.<sup>41</sup> We now have evidence that clinically, adalimumab is an effective and safe treatment option for non-infectious uveitis.<sup>17,18</sup> In the present study, we employ data from VISUAL-1 and VISUAL-2 to evaluate the effect of adalimumab on patient-reported outcomes in patients with non-infectious intermediate, posterior, and panuveitis. In particular, we use NEI-VFQ-25, a reliable and validated measure of visual functioning and general health.

In this analysis, adalimumab-treated patients in VISUAL-1 achieved improvements in 11 of the 12 domains of VFQ-25, as compared to placebo patients. The more substantial improvements were observed in Total Score, General Vision, Ocular Pain, Near Vision and Mental Health. Similarly, adalimumab-treated patients in VISUAL-2 improved in 9 of the 12 VFQ-25 domains, as compared to placebo patients, with significant improvements observed in General Vision and Mental Health.

In addition, the longitudinal analyses performed on both VISUAL-1 and VISUAL-2 indicate that levels of VFQ-25 decrease at a lower rate in adalimumab patients than in placebo patients, suggesting an association between adalimumab treatment and better maintenance of VRQoL. In fact, adalimumab-treated patients in both trials consistently demonstrated greater maintenance of the VFQ-25 composite scores over the last 60 weeks of the trial. These results are important because vision-specific quality of life provides a metric of a patients' vision-related well-being and may be more clinically meaningful than general HRQoL measurement tools.

This study has limitations in that all analyses were performed on a clinical trial population, which may not be representative of the broader uveitis population. As corticosteroids are the standard of care, placebo patients would have instead been treated with corticosteroids outside the trial and may have experienced a different trajectory of visual functioning. The clinical trial contained a heterogeneous uveitis population without information on which groups were responsive to treatment. Also, while the formulation of the longitudinal model was both

parsimonious and flexible, other formulations could be proposed (such as adding spline terms). In fact, the main results presented here were robust to more complex model specifications. Additionally, to increase the statistical power of our analyses, we used the LOCF imputation method, a standard practice in clinical trial analyses. We note, however, that an observed case analysis or other imputation methods can be employed, and that all imputation procedures require assumptions about the underlying missing data mechanism.

In summary, when evaluating novel treatments for uveitis, it is essential to investigate clinical endpoints as well as patient-reported quality of life. The analyses in this manuscript provide evidence that noninfectious uveitis patients treated with adalimumab experience significant and clinically meaningful improvements in VRQoL, compared to placebo. Therefore, adalimumab has become a promising new treatment option, having demonstrated improvements in both clinical and visual functioning outcomes in active and inactive uveitis patients.

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## REFERENCES

1. Jabs D, Nussenblatt R, Rosenbaum J. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509-516.
2. Darrell R, Wagener H, Kurland L. Epidemiology of uveitis: incidence and prevalence in a small urban community. *Arch Ophthalmol*. 1962;68:502-514.
3. Suttorp-Schulten M, Rothova A. The possible impact of uveitis in blindness: a literature survey. *Br J Ophthalmol*. 1996;80:844-848.
4. Nussenblatt R. The natural history of uveitis. *Int Ophthalmol*. 1990;14:303-308.
5. Durrani O, Tehrani N, Marr J, Moradi P, Stavrou P, Murray P. Degree, duration, and causes of visual loss in uveitis. *Br J Ophthalmol*. 2004;88:1159-1162.
6. Thorne JE, Skup M, Tundia N, et al. Direct and indirect resource use, healthcare costs and work force absence in patients with noninfectious intermediate, posterior or panuveitis. *Acta Ophthalmologica*. 2016;94:e331-e339.
7. Dick A, Tundia N, Sorg R, et al. Risk of Ocular Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. *Ophthalmology*. 2016;123(3):655-662.
8. Zierhut M, Deuter C, Murray P. Classification of Uveitis -Current Guidelines. *Touch Briefings*. 2007:77-78.
9. Rodriguez A, Calonge M, Pedroza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. *Arch Ophthalmol*. 1996;114(5):593-599.
10. McCannel C, Holland G, Helm C, Cornell P, Winston J, Rimmer T. Causes of uveitis in the general practice of ophthalmology. UCLA Community-Based Uveitis Study Group. *Am J Ophthalmol*. 1996;121(1):35-46.
11. Barisani-Asenbauer T, Maca S, Mejdoubi L, Emminger W, Machold K, Auer H. Uveitis- a rare disease often associated with systemic diseases and infections- a systematic review of 2619 patients. *Orphanet J Rare Dis*. 2012;7.
12. Jabs D, Akpek E. Immunosuppression for posterior uveitis. *Retina*. 2005;25(1):1-18.
13. Tabbara K. Infectious uveitis: a review. *Arch Soc Esp Ophthalmol*. 2000;75(4):215-259.
14. Jabs D, Rosenbaum J, Foster C, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol*. 2000;130(4):492-513.
15. Cervantes-Castaneda R, Jawed N, Foster C. Immunosuppressive therapy for noninfectious uveitis. *Retin Physician*. 2007:30-37.
16. Becker M, Smith J, Max R, C. F. Management of sight-threatening uveitis: new therapeutic options. *Drugs*. 2005;65(4):497-519.
17. Jaffe G, Thorne J, Scales D, et al. Adalimumab in Patients With Active, Non-infectious Uveitis Requiring High-dose Corticosteroids: the VISUAL-1 Trial. *Investigative Ophthalmology & Visual Science* 2015;56(7):3115.
18. Nguyen Q, Kurup S, Merrill P, et al. Adalimumab in Patients with Inactive, Non-Infectious Uveitis Requiring Systemic Treatment. Paper presented at: ACR/ARHP Annual Meeting 2015.
19. Pasadhika S, Rosenbaum J. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. *Biologics: Targets and Therapy*. 2014;8:67-81.
20. Hui M, Wakefield D, Patel I, Cvejic E, McClusky P, Chang J. Visual Functioning and Health-related Quality-of-Life are Compromised in Patients with Uveitis. *Ocul Immunol Inflamm*. 2016;[Epub ahead of print].
21. Multicenter Uveitis Steroid Treatment (MUST) Trial Follow-up Study Research Group. Quality of Life and Risks Associated with Systemic Anti-inflammatory Therapy versus Fluocinolone Acetonide Intraocular Implant for Intermediate Uveitis, Posterior Uveitis, or Panuveitis: Fifty-

- four-Month Results of the Multicenter Uveitis Steroid Treatment Trial and Follow-up Study. *Ophthalmology*. 2015;122(10):1975-1986.
22. Gui W, Dombrow M, Stowe M, Tessier-Sherman B, Yang E, Huang J. Quality of Life in Patients with Noninfectious Uveitis Treated with or without Systemic Anti-inflammatory Therapy. *Ocul Immunol Inflamm*. 2015;23(2):135-143.
  23. Frick KD, Drye L, Kempen J, et al. Associations among visual acuity and vision- and health-related quality of life among patients in the multicenter uveitis steroid treatment trial. *Invest Ophthalmol Vis Sci*. 2012;53(3):1169-1176.
  24. Murphy C, Greiner K, Plskova J, Frost A, Forrester J, Dick A. Validity of using vision-related quality of life as a treatment end point in intermediate and posterior uveitis. *Br J Ophthalmol*. 2007;91(2):154-156.
  25. Murphy C, Hughes E, Frost A, Dick A. Quality of life and visual function in patients with intermediate uveitis. *Br J Ophthalmol*. 2005;89(9):1161-1165.
  26. Rothova A, Buitenhuis H, Meenken C, et al. Uveitis and systemic disease. *Br J Ophthalmol*. 1992;76:137-141.
  27. Schiffman R. Visual Functioning and General Health Status in Patients With Uveitis. *Arch Ophthalmol*. 2001;119(6):841-849.
  28. Mangione C, Lee P, Gutierrez P, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2001;119(7):1050-1058.
  29. Onal S, Savar F, Akman M, Kazokoglu H. Vision-and health-related quality of life in patients with Behçet uveitis. *Arch Ophthalmol*. 2010;128(10):1265-1271.
  30. Owen C, Rudnicka A, Smeeth L, Evans J, Wormald R, Fletcher A. Is the NEI-VFQ-25 a useful tool in identifying visual impairment in an elderly population? *BMC Ophthalmol*. 2006;6:24.
  31. Revicki D, Rentz A, Harnam N, Thomas V, Lanzetta P. Reliability and Validity of the National Eye Institute Visual Function Questionnaire-25 in Patients with Age-Related Macular Degeneration. *Invest Ophthalmol Vis Sci*. 2010;51(2):712-717.
  32. Naik R, Gries K, Rentz A, Kowalski J, Revicki D. Psychometric evaluation of the National Eye Institute Visual Function Questionnaire and Visual Function Questionnaire Utility Index in patients with non-infectious intermediate and posterior uveitis. *Qual Life Res*. 2013 22(10):2801-2808.
  33. Suner I, Kokame G, Yu E, Ward J, Dolan C, Bressler N. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci*. 2009;50(8):3629-3635.
  34. Ziegler A, Vens M. Generalized estimating equations. Notes on the choice of the working correlation matrix. *Methods Inf Med*. 2010;49(5):421-425.
  35. Loftus E, Feagan B, Colombel J, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *The American journal of gastroenterology*. 2008;103(12):3132-3141.
  36. Revicki D, Willian M, Saurat J, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2008;158(3):549-557.
  37. Mittendorf T, Dietz B, Sterz R, Kupper H, Cifaldi M, von der Schulenburg J. Improvement and longterm maintenance of quality of life during treatment with adalimumab in severe rheumatoid arthritis. *J Rheumatol*. 2007;34(12):2343-2350.
  38. van der Heijde D, Kivitz A, Schiff M, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2006;54(7):2136-2146.
  39. Gladman D, Mease P, Ritchlin C, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum*. 2007;56(2):476-488.

40. Sandborn W, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142(2):257-265.
41. Armstrong A, Pinsky B, Sundaram M, Shu L, Okun M, Bao Y. Adalimumab improves health-related quality of life (HRQoL) in patients with moderate to severe hidradenitis suppurativa (HS): Results from the first 12 weeks of PIONEER II. *J Am Acad Dermatol*. 2015;72(5):AB38.
42. Mangione C. The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25). 2000.